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14. ABSTRACT

The purpose of this study was to evaluate the predictors of breast cancer outcomes using a multidisciplinary approach. Specifically, we evaluated the epidemiologic And genetic factors affecting survival and contra-lateral breast cancer (CBC) risk among women with different types of breast cancer (based on histology) and how these factors interacted with breast cancer treatment. To accomplish these aims, we evaluated survival and CBC risk among an ongoing cohort of 18,270 breast cancer cases recruited into a series of multi-state ease- control studies of breast cancer conducted from 1988-2001.

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breast cancer, epidemiology, histology, survival

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Introduction

Following a diagnosis of breast cancer, women are faced with numerous important concerns, two of which are understanding their chances of survival and their risk of contralateral breast cancer (CBC, a second primary tumor in the other breast). While significant advances in knowledge have been made in understanding the relationship of environmental and genetic factors with breast cancer etiology and prevention, much less is known about how these factors affect survival after diagnosis or risk of CBC. Evidence suggests that tumor grade and lymph node status, which reflect the tumor's aggressiveness and spread, do not completely explain breast cancer outcomes [1]. In addition, the majority of breast cancer studies have failed to take into account the heterogeneity of the disease. Two ways of categorizing breast cancer that have etiologic and clinical important are by histologic type and estrogen receptor (ER)/progesterone receptor (PR) status, but little is known about how epidemiologic and genetic factors influence survival and risk of CBC across these categories. Understanding how epidemiologic and genetic factors affect survival and risk of CBC across these categories and in conjunction with various treatment regimens, may not only provide women with breast cancer with ways to positively affect the course of their disease, but may also provide important information for physicians and public health professionals to draw from when developing strategies for the care of future breast cancer cases. The purpose of this study was to evaluate epidemiologic and genetic factors affecting survival and CBC risk among women with different types of breast cancer (based on histology and ER/PR status) and how these factors interact with breast cancer treatments. To address these aims, we proposed to evaluate survival and CBC risk among an ongoing cohort of 18,270 breast cancer cases recruited into a series multi-state (Wisconsin, Massachusetts, and New Hampshire) case-control studies of breast cancer conducted from 1988-2001.

Specific aims that were addressed included:

1) Assessing the relationship between breast cancer risk factors (such as obesity, physical activity, alcohol use, and postmenopausal hormones) and length of survival among women diagnosed with lobular vs. ductal breast cancers.
2) Assessing the association of common genetic variants in DNA repair and estrogen metabolisms genes, as well as their interaction with different treatments (chemotherapy, radiotherapy, hormonal therapy), in relation to survival among women diagnosed with lobular vs. ductal breast cancer
3) Assessing the relationship between known breast cancer risk factors and risk of CBC.
4) Evaluating whether the relationship between breast cancer risk factors and risk of CBC differed among women diagnosed with lobular vs. ductal breast cancer
5) Assessing the association of common genetic variants in DNA repair and estrogen metabolism genes, as well as their interactions with various treatments in relation to risk of CBC.

Body

[redacted]

The following is the approved SOW (statement of work) for Grant # W81XWH-05-1-03115.

Survival and Risk of Contralateral Breast Cancer: Epidemiology, Genetics, and Histopathology

Task 1: Attend coursework to obtain cross-training in genomics and pathology, Months 1-12:

a. Attend formal courses at the University of Washington in molecular biologic, genetics, and pathology.

Task 2: Complete a laboratory practicum in the breast cancer pathology laboratory of Dr. Peggy Porter, Months 1-12:
a. Learn methods of tissue procurement, handling, and preparation
b. Observe and practice techniques for characterizing genes and gene products, including immunohistochemistry, in situ hybridization, and flow cytometry.

Task 3: Complete a laboratory practicum in the Core Genotyping Facility at NCI under direction of mentor Dr. Stephen Chanock (1.5-2 months, in Year 2 or 3):
a. Learn advanced methods of DNA sequencing, high throughput genotyping, and other techniques of genetic characterization.

Task 4: Attend seminars, journal clubs, and professional meetings to learn about latest research in breast cancer biology, Months 1-36:
a. Attend organized seminars in the departments of genetics, cancer biology, statistical genetics, and epidemiology through the University of Washington and the FHCRC.
b. Attend bi-monthly seminar series organized by the FHCRC Breast Cancer Program.

Task 5: Linkages to the National Death Index and State Tumor Registries, Months 1-24:
a. Work with University of Wisconsin programmers and administration at NDI to follow-up breast cancer cases enrolled in the CBCS study for any cause and breast cancer death.
b. Work with University of Wisconsin programmers and administration at state tumor registries to follow-up breast cancer cases enrolled in CBCS study for second primary breast cancers (contralateral breast cancer).

Task 6: Genotyping of polymorphisms in estrogen metabolism, Months 12-18:
a. In collaboration with Drs. Chanock and Garcia-Closas (NCI), select appropriate commercial facility to conduct genotyping of polymorphisms in estrogen metabolism.

Task 7: Interim Analyses, Months 18-30:
a. Data cleaning, variable definitions
b. Merging of outcomes data (from linkages) and genetic data (from genotyping) to collected epidemiologic risk factor data.
c. Preliminary data analyses, preparation of preliminary results for abstracts to present at national meetings

Task 8: Final Analyses and Manuscript Preparation, Months 30-36:
a. Attend DOD-sponsored meeting to present preliminary work.
b. Additional data analysis using epidemiologic data from interviews, pathologic information from cancer registries, and genetic information from laboratory work.
c. Prepare final report and initial manuscripts for publication

Due to personnel changes, the scope and duration of award has been changed, and the contracted was terminated effective 31 January 2006 (original termination date 27 February 2008). However, during months 1-11 of the contract, significant progress was made towards accomplishing the tasks slated for year 1 as well as some portions of tasks for later years.

Tasks 1 & 2: Attend coursework to obtain cross-training in genomics and pathology. Complete a laboratory practicum in the breast cancer pathology laboratory of Dr. Peggy Porter

Regrettably, there are two tasks that were to be completed in Months 1-12 that have not yet been. The first, coursework in genomics and pathologic, was not completed because the proposed courses were not offered during the Spring, Summer, or Fall Quarters of year 1 (the

first funded academic year of the grant). Prior to the termination of the grant, consultations with mentors were underway to select appropriate substitute courses. The second, a laboratory practicum in breast cancer pathology in Dr. Porter's lab, was not completed due to scheduling conflicts and work overload in her lab. Plans for rescheduling the practicum had not been undertaken prior to the termination of the grant.

Task 3: Complete a laboratory practicum in the Core Genotyping Facility at NCI under direction of mentor Dr. Stephen Chanock (1.5-2 months, in Year 2 or 3):

Slated to begin in either year 2 or year 3 of grant, this task was not begun.

Task 4: Attend seminars, journal clubs, and professional meeting to learn about latest research in breast cancer biology, Months 1-36.

Dr. Morimoto attended regular meetings of various seminars and journal clubs at the FHCRC, including the Breast Cancer Seminar Series, cross-disciplinary series of talks taking place twice a month at the Seattle Cancer Care Alliance, the Interdisciplinary Club, and the Molecular Epidemiology Discussion Group. In addition, she attended two national/international professional meetings: 1) The American Society of Preventive Oncology Annual Meeting 2005, San Francisco, CA, where she presented preliminary results from this project, entitled "Postmenopausal Hormone Therapy and Risk of Mortality From Invasive Breast Cancer By Histologic Type and Stage"; 2) The 4th Era of Hope meeting for the Department of Defense Breast Cancer Research Program 2005 (Philadelphia, PA).

Task 5: Linkages to the National Death Index and State Tumor Registries, Months 1-24:

During Months 1-11 of this contract, linkages to the National Death Index to follow-up for death outcomes for all women in the CBCS cohort through December, 2004. Linkage to the Wisconsin Cancer Registry to follow-up for new cancer outcomes (including second primary breast cancers) has been completed for Wisconsin members of the cohort. The application to the Massachusetts State Cancer Registry and IRB approval at relevant institutions has been completed, and linkage is underway, to follow-up Massachusetts cohort members for new cancer outcomes.

Task 6: Genotyping of polymorphisms in estrogen metabolism, Months 12-18:

Genotyping for polymorphisms in estrogen metabolism and DNA repair are underway and some have already been completed (this task for slated to begin in year 2). Candidate genes for genotyping included *BRCA2, RAD51, XRCC1, XRCC3, BRIP1, ESR1,* and *SULT1A1.* At the time of grant termination, polymorphisms in *BRCA2, XRCC3,* and *ESR1* have been completed and preparation for genotyping of *SULT1A1* polymorphisms were underway.

Task 7: Interim Analyses, Months 18-30:

Significantly ahead of schedule, interim analyses for the survival portion of the grant have been completed (this was possible because linkages to NDI preceded those to the relevant state cancer registries). Outcomes data from linkage with the NDI has been merged with the covariate dataset. The data set has been cleaned, algorithms for established breast cancer risk factors have been developed and programmed, and important exposure variables have been created. Preliminary data analyses for survival has been completed (some of results has been submitted and presented at a national meeting—see task #2).

Task 8: Final Analyses and Manuscript Preparation, Months 30-36:

Final analyses for some portions of the survival analyses have been completed and manuscripts are being prepared. Specifically, a manuscript titled "Hormonal and Reproductive Factors in Relation to Survival from Invasive Ductal and Lobular Breast Cancer" is in the final stages of completion. Key findings from this analysis are listed below (in the "Key Research Accomplishments" section). The final analysis for the relationship of alcohol consumption and survival by histologic type has been completed, although manuscript preparation was not yet underway at the time of grant termination.

Key Research Accomplishments:

The following summarizes the key research findings up to the time of grant termination:

Postmenopausal hormone (PMH) use and survival by histologic type

- Use of estrogen-only regimens of PMH significantly reduced mortality among women diagnosed with lobular cancer (HR=0.60 (0.37-0.98)); this effect was particular strong among women who were current users at the time of diagnosis (HR=0.38 (0.19-0.78)).
- Use of estrogen-only regimens was unrelated to survival from ductal cancers.
- Use of combined estrogen-progestin PMH regimens reduced mortality from ductal cancer among women who had ever used them (HR=0.67 (0.67-0.92)) and users at the time of diagnosis (HR=0.70 (0.49-1.00)). While this reduction was also observed among current users for lobular cancers (HR=0.37 (0.16-0.86)), there was no significant association with ever use.

Body mass index (BMI)

- The heaviest women at diagnosis had a statistically significantly increased risk of death from ductal cancers, but not from lobular cancers. This difference between the subtypes, however, was not statistically significant.

Alcohol consumption

- Women who frequently consumed alcoholic beverages (7+ drinks/week) at the time of diagnosis had an increased risk of mortality from lobular tumors. Alcohol consumption was unrelated to risk of death from ductal tumors.

Reportable Outcomes

One accepted and presented abstract resulted from the research to date. Titled "Postmenopausal Hormone Therapy and Risk of Mortality From Invasive Breast Cancer By Histologic Type and Stage," it was presented at the American Society for Preventive Oncology Annual Meeting 2005 (San Francisco, CA) and has been included in this report.

Conclusion

Due to its early termination, all research aims of this grant have not been completed at the time of this final report. However, preliminary results suggest that lobular and ductal breast cancers, in addition to have different risk factors, may also have different relationships to survival factors, particularly with respect to PMH use and alcohol consumption. Additional research is required to explore how these and other modifiable factors affect other outcomes, such as contralateral breast cancer risk, and how this knowledge may be used to help identify subpopulations of breast cancer survivors who may benefit from certain lifestyle modifications or treatments.

References

1) Schemper, M. The relative importance of prognostic factors in studies of survival. Stat Med, *12:* 2377-82, 1993.

Appendices

1) ASPO accepted abstract
2) ASPO poster presentation

Supporting Data

N/A

AMERICAN SOCIETY OF PREVENTIVE ONCOLOGY - ABSTRACT FORM

For Submission of Presented Papers at the 29th Annual Meeting in San Francisco, CA, March 13-15, 2005.

An abstract, consisting of 150-200 words, **MUST fit** in the box below. Title should be brief and clearly state content of paper. Please list last names and first initials of co-authors. The body of the abstract should be organized as follows: **1.** Purpose of study (one sentence if possible). **2.** Simple statement of methods. **3.** Summary of results (adequate to support conclusion). **4.** Statement of conclusions. (Do not use phrases such as "The results will be discussed.") **5.** No illustrations are permitted within abstracts. Space is allocated to publish the top-ranked abstracts in the February 2005 issue *of Cancer Epidemiology, Biomarkers and Prevention.*

I would like to present this abstract as:

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Please check the category in which you wish to have this abstract considered for either oral or poster presentation:

- ☒ Cancer Epidemiology
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or
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Type abstract below – STAY WITHIN THE BORDERS.

Postmenopausal hormone therapy and risk of mortality from invasive breast cancer by histologic type and stage. L. Morimoto, C. Li, A. Trentham-Dietz, P. Newcomb. (Fred Hutchinson Cancer research Center, Seattle, WA 98109; University of Wisconsin, Madison WI 53726).

Some observational studies suggest that use of postmenopausal hormones (PMH) prior to the diagnosis of invasive breast cancer is associated with less advanced tumors and improved survival. However, results from the Womens Health Initiative randomized controlled trial of estrogen and progesterone indicate that PMH users are more likely to have tumors that are larger and of a more advanced stage compared to non-users. These differences may be attributable differential screening in the general population by PMH use. In a cohort of >11,000 women diagnosed with breast cancer from 1988-2001 in Wisconsin, we examined the relationship between PMH use and survival by tumor stage and histology. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were obtained using Cox regression. Among women diagnosed with advanced stage (regional/distant) tumors, PMH use was associated with improved survival among women with both ductal (HR=0.63; 95% CI: 0.78-0.83) and lobular (HR=0.47; 95% CI: 0.25-0.88) carcinomas. Alternatively, PMH was not associated with survival among women with local stage tumors. It is unclear why PMH users have a lower risk of mortality than do non-users, though this may be simply due to improved access to care for PMH users, or to a true biologic effect of PMH use.

FAX Copies are NOT acceptable!

Type information below for the **AUTHOR** who will be **PRESENTING** the work at **ASPO:**

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ABSTRACT DEADLINE: OCTOBER 18, 2004.

Postmenopausal Hormone Therapy and Risk of Mortality From Invasive Breast Cancer By Histologic Type and Stage

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University of Wisconsin Comprehensive Cancer Center, Madison, WI

FRED HUTCHINSON CANCER RESEARCH CENTER

BACKGROUND

The two most common histologic types of breast cancer are invasive ductal carcinoma and invasive lobular carcinoma. Approximately 80% of breast cancers diagnosed in the U.S. are ductal cancers, yet incidence rates of lobular have increased rapidly over the past two decades, such that ILC now accounts for approximately 15% of all U.S. cases.[1] Risk factors for breast cancer do vary by histologic type, with the most notable example being use of combined estrogen and progestin (E+P) therapy by postmenopausal women. Several studies have shown that use of E+P is more strongly associated with an increased risk of lobular cancers than it is with risk of ductal cancers. However, little is known about how risk factors relate to survival among women diagnosed with different histologic subtypes of tumors.

METHODS

Design:
Population-based prospective cohort study

Study Subjects:
Subjects were incidence invasive breast cancer cases identified through the Wisconsin Cancer Reporting System (WCRS), a population-based cancer registry between 1984-2000. Our cohort consisted of 9,231 women (75,842 person-yrs), of which 7997 had ductal histology (66,224 person-yrs) and 1,234 had lobular or mixed lobular and ductal histology (9,618 person-yrs).

Exposure data:
All cases completed the standard CBCS interview that elicited details on breast cancer risk factors prior to and at diagnosis, including demographics, reproductive experiences, body size, and medication use including PMH use. Information on tumor characteristics, including histology, and first course of treatment were obtained from WCRS.

Survival data:
Follow-up information was ascertained through linkage with Wisconsin death certificates. The length of follow-up time was measured as the time from diagnosis of breast cancer to: death from breast cancer; date of last follow-up; or the end of the study period (December 2002), whichever occurred first.

Analysis:
Associations between risk factors and mortality from breast cancer were estimated using Cox proportional hazards regression. All analyses were adjusted for age, stage at diagnosis, education, and type of treatment.

RESULTS

There was no significant difference in overall survival comparing women with ductal vs. lobular/mixed tumors (HR=0.9 (0.8-1.1)).

Table 1:
- Women who died of lobular/mixed tumors were more likely to be premenopausal, heavier at diagnosis, frequent alcoholic beverage drinkers, and former or current users of PMH, relative to those who died of ductal tumors.

Table 2:
- Among both ductal and lobular/mixed cases, advanced stage was dramatically associated with mortality.
- There was a suggestion that being a frequent alcoholic beverage drinker was associated with mortality among lobular/mixed cases, but not among ductal cases (p-interaction=0.09).
- Among women with lobular/mixed tumors, being diagnosed after menopause was more strongly associated with mortality than among women with ductal tumors.

Table 3:
- Among women with ductal carcinomas, advanced age at diagnosis was slightly positively associated with mortality from advanced stage tumors, but slightly inversely associated with mortality from local tumors (p-interaction=0.01). This association was not observed among women with lobular/mixed tumors.
- There was a suggestion that being heavier at diagnosis was associated with poorer survival among local lobular/mixed tumors, but not for advanced lobular/mixed tumors.
- Among women with local lobular/mixed tumors, being a current or former PMH use was associated with increased mortality, but among those with advanced lobular/mixed tumors, it was associated with reduced mortality. This trend was observed among women with ductal tumors as well, although the interaction was significant only for estrogen plus progestin formulations.

RESULTS

Table 1: Comparison of various characteristics among 7,997 ductal cases and 1,234 lobular/mixed cases

	Ductal		Lobular/Mixed	
	# at risk	# of deaths (%)	Total N	# of deaths (%)
Stage				
Local	5067	309 (6)	743	36 (5)
Regional	2346	544 (23)	405	83 (20)
Distal	147	93 (63)	34	19 (56)
Age				
<50	1676	231 (14)	206	23 (11)
50-60	2208	267 (12)	333	39 (12)
60-70	2786	323 (12)	454	49 (11)
70-80	1327	177 (13)	241	32 (13)
Menopausal status				
Pre	1830	233 (13)	233	21 (9)
Post	5782	722 (12)	938	116 (12)
Unknown	385	43 (11)	63	6 (10)
BMI				
<22.5	1948	268 (14)	308	29 (9)
22.5-25.1	1963	239 (12)	281	48 (17)
25.1-28.9	1938	218 (11)	307	26 (8)
28.9+	1947	246 (13)	306	34 (11)
Alcoholic beverages/week				
0-1	4038	504 (12)	645	65 (10)
1-7	2788	357 (13)	402	50 (12)
7+	1057	116 (11)	174	25 (14)
Any HRT				
Never	4853	640 (13)	728	88 (12)
Former	635	84 (13)	91	17 (19)
Current	1655	119 (7)	320	24 (8)
Estrogen-only				
Never	4853	640 (13)	728	88 (12)
Former	395	49 (12)	60	10 (17)
Current	801	68 (8)	140	10 (7)
Estrogen+progesterone				
Never	4853	640 (13)	728	88 (12)
Former	93	9 (10)	15	3 (20)
Current	688	34 (5)	150	12 (8)
Family history of BrCA				
No	6135	792 (13)	941	111 (12)
Yes	1634	174 (11)	257	26 (10)
Unknown	228	32 (14)	36	6 (17)

Table 2: Risk of breast cancer mortality by histologic subtype

	Ductal		Lobular/Mixed	
	HR	95% CI	HR	95% CI
Age				
<50	1.0		1.0	
50-60	0.9	0.7-1.1	1.1	0.7-1.9
60-70	1.0	0.8-1.1	1.1	0.6-1.9
70-80	1.0	0.8-1.2	1.3	0.7-2.4
Stage				
Local	1.0		1.0	
Regional	3.7	3.2-4.3	4.3	2.8-6.4
Distal	14.4	11.2-18.5	18.7	10.2-34.1
Family history of BrCA				
No	1.0		1.0	
Yes	0.9	0.7-1.0	0.9	0.6-1.4
Alcoholic beverages/week				
0-<1	1.0		1.0	
1-7	1.1	0.9-1.2	1.1	0.8-1.6
7+	0.9	0.7-1.1	1.5	0.9-2.4
BMI				
<22.5	1.0		1.0	
22.5-25.1	0.9	0.7-1.0	2.0	1.2-3.2
25.1-28.9	0.9	0.8-1.1	0.8	0.5-1.5
28.9+	1.0	0.8-1.2	1.2	0.7-2.1
Any HRT				
Never	1.0		1.0	
Ever	0.8	0.7-1.0	0.9	0.6-1.3
Former	1.0	0.8-1.3	1.5	0.8-2.6
Current	0.8	0.6-0.9	0.7	0.4-1.1
Estrogen-only				
Never	1.0		1.0	
Ever	0.9	0.7-1.1	0.9	0.5-1.5
Former	1.0	0.7-1.4	1.2	0.6-2.5
Current	0.8	0.6-1.1	0.7	0.3-1.4
Estrogen+progesterone				
Never	1.0		1.0	
Ever	0.8	0.6-0.9	0.9	0.5-1.8
Former	0.8	0.4-1.8	1.8	0.5-5.5
Current	0.6	0.4-0.9	0.8	0.4-1.7
Menopausal status				
Pre	1.0		1.0	
Post	1.2	0.9-1.5	2.1	1.0-4.5

* adjusted for age, stage, education, and treatment

Table 3: Risk of breast cancer mortality by histologic subtype and by stage of disease at diagnosis

	Ductal Carcinoma				Lobular & Mixed			
	Local		Regional/Distant		Local		Regional/Distant	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age								
<50	1.0		1.0		1.0		1.0	
50-60	0.8	0.6-1.2	0.9	0.8-1.2	1.3	0.3-5.0	1.1	0.6-1.9
60-70	0.7	0.5-1.0	1.1	0.9-1.4	2.6	0.7-9.4	0.8	0.5-1.6
70-80	0.6	0.5-1.2	1.2	0.9-1.6	1.2	0.3-4.9	1.5	0.7-2.9
p-trend	0.19		0.09		0.67		0.50	
p-interaction		0.01				0.87		
BMI								
<22.5	1.0		1.0		1.0		1.0	
22.5-25.1	0.9	0.7-1.3	0.9	0.7-1.1	3.7	1.3-10.5	1.6	0.9-2.7
25.1-28.9	1.0	0.8-1.4	0.9	0.7-1.1	1.8	0.6-5.6	0.5	0.3-1.0
28.9+	1.3	0.9-1.7	0.9	0.8-1.2	3.1	1.1-9.1	0.8	0.5-1.5
p-trend	0.14		0.73		0.12		0.08	
p-interaction		0.48				0.08		
Any HRT								
Never	1.0		1.0		1.0		1.0	
Ever	1.0	0.7-1.3	0.7	0.6-0.9	1.7	0.8-3.5	0.7	0.4-1.1
Former	1.0	0.6-1.5	1.0	0.7-1.3	2.4	0.9-6.6	1.3	0.7-2.5
Current	1.0	0.7-1.3	0.6	0.5-0.8	1.9	0.6-3.4	0.5	0.2-0.9
p-interaction		0.14				0.03		
Estrogen-only								
Never	1.0		1.0		1.0		1.0	
Ever	1.1	0.8-1.5	0.8	0.6-1.0	2.1	0.9-5.0	0.6	0.3-1.1
Former	1.2	0.7-1.9	0.9	0.6-1.3	2.5	0.8-7.8	0.8	0.3-2.1
Current	1.0	0.7-1.5	0.7	0.5-1.0	1.9	0.7-5.4	0.4	0.2-1.1
p-interaction		0.44				0.04		
Estrogen+progesterone								
Never	1.0		1.0		1.0		1.0	
Ever	0.8	0.6-1.5	0.4	0.3-0.7	1.6	0.5-4.9	0.6	0.3-1.4
Former	0.6	0.1-2.4	0.8	0.3-2.0	5.4	0.7-45.1	1.4	0.3-6.1
Current	1.0	0.6-1.7	0.4	0.2-0.7	1.4	0.4-4.5	0.6	0.2-1.3
p-interaction		0.05				0.29		

* adjusted for age (categorical), education, and treatment

CONCLUSIONS

Ductal and lobular/mixed tumors share similar risk factors affecting mortality
However, when taking stage at diagnosis into consideration, these risk factors differ.

Frequent alcohol drinks experience a 50% increased risk of mortality from lobular/mixed tumors
- In a previous study[2], frequent alcohol consumption was more related to increased risk of lobular/mixed tumors than ductal.
- The association with lobular/mixed mortality and alcohol consumption may reflect a continuation of these habits.

PMH use was associated with improved survival among women diagnosed with advanced tumors, but not local tumors
- This observation does not seem to be due to screening, since women on PMH use might be expected to have more frequently screening, and subsequently, earlier stage tumors.
- The associations with PMH use differed by histologic type: E-only formulations were more protective for advanced lobular/mixed tumors, while E+P formulations were more protective for ductal tumors.
- These observations are paradoxical: in etiologic studies, E+P was more strongly related to increased risk of lobular tumors (relative to ductal).

LIMITATIONS

Small numbers of women with lobular/mixed histology tumors
- However, we plan to add additional CBCS data (from MA and NH) as well as updated survival information, which will improve our statistical power.

Incomplete information on ER/PR status of tumors
- We are currently in the process of collecting ER/PR data on the majority of tumors, and we plan to conduct analyses stratified by ER/PR status.

No data on exposures after diagnosis
- Post-diagnosis exposures may affect disease progression and therefore survival, and our inability to assess these exposures may have biased our estimates.

LITERATURE CITED

1. Li CI et al. JAMA 2003;289:1421-1424.
2. Li CI et al. Cancer Epidemiol Biomark Prev 2003;12:1061-6.

SUPPORT

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